WHO Technical Advisory Group on Innovations in Male Circumcision

Report of teleconferences October 2018 and June 2019

Key Populations and Innovative Prevention, Department of HIV and Hepatitis, World Health Organization, Geneva Switzerland, September 2019

Suggested citation. Technical Advisory Group on innovations in male circumcision. Report of teleconference October 2018 and June 2019. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO.

Contents

Abbreviations

AE	adverse event
CI	confidence interval
FRP	foreskin removal procedure
IM	intramuscular
MC	male circumcision
RCT	randomized controlled trial
TAG	Technical Advisory Group on Innovations in Male Circumcision
TT	tetanus toxoid
TTCV	tetanus toxoid-containing vaccination
WHO	World Health Organization

Introduction

In October 2018 the World Health Organization (WHO) Technical Advisory Group (TAG) on Innovations in Male Circumcision held a teleconference to consider updates on the clinical evaluations of 1) the elastic collar compression device[1] Day_0 foreskin removal procedure, designed to mitigate tetanus risk associated with the standard Day_7 elastic collar compression device method, and 2) the vice clamp surgical assist device (see Annex 1. Agenda and Annex 2. List of participants). A follow up virtual TAG consultation was undertaken in June 2019 with the purpose to review additional expert opinions provided by the manufacturer of one device.

The WHO Secretariat opened the teleconference and introduced the members present as well as the external consultant on tetanus.

All TAG members and consultants were reminded that some information shared with TAG is confidential and not publicly available. TAG members were asked to maintain this confidentiality in accordance with their signed confidentiality agreements. Each member was asked in turn to declare verbally any potential interests related to the subject of the teleconference. All members responded that they had no interests to declare.

The key discussion points and recommendations from the consultation were to be shared with the WHO Guideline Development Group meeting in November 2018 and would be used to inform the WHO male circumcision device prequalification process.

TAG co-chair Tim Hargreave was asked to lead the meeting.

Elastic collar compression device[1] Day_0 foreskin removal procedure

Clinical data and reports

Reports were reviewed on the clinical safety of the Day_0 foreskin removal procedure (Day_0 FRP) from the first study in Zambia (no new information was added to the report reviewed in September 2017) and three new studies – two conducted in Kenya and one in Rwanda. These reports were supplemented with a specially commissioned expert review, presented in the report *Voluntary medical male circumcision and tetanus risk* (Annex 3).

The clinical reports included a total of 1507 placements from the four studies, all of which followed a common protocol for foreskin removal approximately 30 minutes after device placement (thus, Day_0), with the device then removed seven days after placement. Day_0 FRP was developed during the Zambia study as an alternative to the standard Day_7 foreskin removal procedure (Day_7 FRP), in which the foreskin and device together are removed seven days after device placement. Day_0 placements numbered 381 in the second phase of the Zambia study, 101 in a randomized trial (Kenya) comparing Day _0 with the Day 7 FRP and two field studies - in Kenya (515 clients) and in Rwanda (510 clients (Table 1). The RCT compared the 101 Day_0 FRP clients with 42 Day_7 FRP clients.

The procedure to prepare for device removal after seven days varied somewhat across the studies. In Zambia the instructions were for the client to wet his penis by dampening a piece of paper towel with clean water and holding it wrapped around the device for at least 20 minutes. These same instructions

[1] PrePex

were annexed to the reports from the other sites, but the Kenya RCT report stated that, in addition to the dampened paper towel, wet gauze soaked in povidone iodine was applied for about five minutes before device removal, and the Kenya field study stated that gauze soaked in normal saline was applied for 10 minutes.

Across the four studies a total of 13 adverse events (AEs) were reported among the 1507 Day_0 FRP clients following revision of the Zambia foreskin removal protocol, for a risk rate of 0.9%. This rate is substantially less than the rate of 5.9% in Zambia Phase 1 (seven AEs reported in the first 119 placements). Of these 13 AEs, 10 occurred within the first week – severe bleeding immediately or soon after foreskin removal (6), self-removals on Day 2 (2), bleeding on Day 2 (1) and bleeding controlled with pressure (day relative to device placement or removal not reported) (1). The three remaining AEs occurred after removal of the device on Day 7; they included two wound infections treated with oral antibiotics and one tetanus case.

The tetanus case was documented in the Kenya field study report, which included clinical reports, notes, expert opinions and correspondence about this case. This client had received a tetanus toxoid-containing vaccination (TTCV) dose at the time of device placement. The patient was admitted to hospital on Day 22 after device placement (Day 15 after device removal). Symptoms had first appeared five days before hospitalization. He was treated with intramuscular (IM) diazepam, IM ceftriaxone and human tetanus immune globulin. He was discharged four days later.

Table 1. Clinical data on elastic collar compression Day_0 foreskin removal procedure

Study	Design	Period	Number	Adverse events	Remarks	TTCV provision*
Zambia Phase 1	Cohort	Mar 2017	119	7	Pilot phase, first assessment of Day_0 FRP	None
Zambia Phase 2	Cohort	Mar 2017	381	3	Revised Day_0 FRP protocol	None
Kenya randomized controlled trial	Day_0 FRP versus Day_7 elastic collar compression removal procedure	Apr–Aug 2017	101	2	Day_0 FRP protocol as in Zambia Phase 2 cohort	1 dose at time of placement
			42 with Day_7 foreskin and device removal	1		2 doses before placement**
Kenya field study	Cohort	Sep–Nov 2017	515	4	Day_0 FRP protocol as in Zambia Phase 2 cohort	1 dose at time of placement
Rwanda field study	Cohort	Oct–Nov 2017	510	4	Day_0 FRP protocol as in Zambia Phase 2 cohort	2 doses before placement**

FRP = foreskin removal procedure; TTCV = tetanus toxoid-containing vaccination

* Information added after TAG discussion

** Two doses at least four weeks apart, with the second at least two weeks before device placement (WHO-recommended protocol)

The TAG considered key points from the expert consultant's review on tetanus risk with different circumcision methods (Annex 3), which incorporated reviews by a clinician with expertise in several thousand tetanus cases and a microbiologist. The expert consultant discussed the new tetanus case. Although there was some uncertainty about the diagnosis, she concluded that the case should be classified as being consistent with a causal association (signs and symptoms of tetanus within a plausible incubation period, with reportedly normal wound healing and no alternative tetanus entry points evident elsewhere on the body).[1] She also noted that the circumcision clients in the Rwanda cohort had all received two TTCV injections before device placement in accordance with WHO recommendations and were likely protected from tetanus. They could not be considered in the "at risk" denominator when assessing tetanus incidence.

Summary points and recommendations

Key points and recommendations from the TAG emanated from the June 2018 meeting. An additional opportunity in June 2019 was provided to review additional expert opinions provided by the manufacturer. The June 2019 feedback showed consensus that the summary points should not be altered. These points are:

- The main safety concern of the Day_0 foreskin removal procedure was bleeding during the first week after placement and before device removal on Day 7. The proportion of clients experiencing an adverse event (10 in 1507 placements, or 7 per 1000 placements, 95% confidence interval (CI) 3 to 12 per 1000) appeared similar to the proportion observed with the Day_7 device and foreskin removal procedure, although the timing and clinical nature of the AEs differed.
- The clinical presentation and course of the tetanus case was considered consistent with mild tetanus. The clinical notes and examinations did not identify any wounds or other potential sites of infection other than the recent circumcision procedure.
- It was considered that the patient would likely have received tetanus toxoid injections as an infant through the routine vaccination programme, and the dose given at the time of device placement may have provided a booster response that contributed to the successful treatment outcome.
- The two study reports from Kenya also referred to TTCV prior to device placement. The TAG members requested a more thorough analysis of the number of Day_0 FRP clients according to their TTCV history and a comparison with previous information on tetanus risk, specifically incidence based on TTCV provision for study participants.
    - The one mild tetanus case had occurred in a total of 616 clients with one TTCV dose at placement and 500 clients with none. The incidence was approximately 90 per 100 000 procedures (95% CI 2.3 to 500) in clients about half of whom may have had partial protection from tetanus and half of whom may have had no or insufficient protection. This compared with approximately five cases per 100 000 Day_7 procedures and 0.2 cases

[1] WHO Informal Consultation on Tetanus and Voluntary Medical Male Circumcision: Report of meeting convened in Geneva, Switzerland, 9–10 March 2015. Geneva, World Health Organization, 2015. https://www.who.int/hiv/pub/malecircumcision/tetanus-male-circumcision/en/.

per 100 000 conventional surgical circumcisions, all in clients with no TTCV injections at the time of or prior to circumcision.[1]

- It was considered that there was no evidence of lower tetanus risk with the new Day_0 FRP protocol than with the Day_7 procedure.
- It was **recommended** that no modification should be made to the previous advice[1] that clients be fully protected against tetanus by vaccination before placement of the elastic collar compression device.
- The clinical data on Day_0 FRP was considered promising, and it was **recommended** that further use and clinical monitoring of safety, acceptability and reproducibility be undertaken in settings where proper tetanus protection, per WHO guidance, could be assured.
- Minor variations were noted in the removal procedures among the different studies and that some removals had been quite difficult, possibly due to desiccated foreskin remnants preventing easy inner ring extraction. Further exploration was recommended of good device removal procedures after foreskin excision on Day_0.
- The findings were to be shared with the meeting of the WHO Guideline Development Group (on Updated recommendations on safe male circumcision for HIV prevention and related service delivery for adolescent boys and men in generalized HIV epidemics) in November 2018 for their perspective on tetanus risk, tetanus risk mitigation and circumcision method.

Vice clamp surgical assist circumcision device

The vice clamp[2] surgical assist device is based on the Gomco surgical assist device extensively used for paediatric circumcision and tried in adults in a study in Mozambique. The device provides a firm and extended (at least five minutes) crush of the foreskin, sufficient to prevent bleeding. In adults in Mozambique cyanoacrylate tissue adhesive and a firm adhesive bandage applied after device removal were sufficient to control post-operative bleeding. Problems with reuse of the Gomco devices and mismatching of parts led to the concept of a single-use disposable device, subsequently strengthened to increase the crushing force. This device – version #2 – was evaluated in a series of five studies in South Africa with a total of 543 clients, 127 of whom were adolescents ages 10–15 years (Table 2).

Table 2. Clinical data on vice clamp surgical assist device version #2

Study	Design (location and period)	Number	Remarks
Unicirc Study 2	Case series (Cape Town, South Africa, 2013)	50	First study with modified version #2 device
Unicirc Study 3	Field study (3 sites in South Africa, 2014)	110	
Unicirc Study 4	Randomized controlled trial (2 sites, South Africa, 2015)	50	Plus control arm with 25 conventional surgical circumcisions (with injectable anaesthesia. All vice clamp clients received topical anaesthesia.)

[1] Tetanus and voluntary medical male circumcision: risk according to circumcision method and risk mitigation. Report of the WHO Technical Advisory Group on Innovations in Male Circumcision – consultative review of additional information, 12 August 2016. Geneva, World Health Organization, 2016. https://apps.who.int/iris/handle/10665/250146.

[2] Unicirc

Unicirc Study 5	Adolescent study (1 site, South Africa, 2016)	82	Adolescents ages 10–15 years
Registry	Circumcision at 1 site (South Africa, 2016–17)	251	Including 45 adolescents ages 10–15 years
Total		**543**	**Including 127 ages 10–15 years**

The totality of clinical data over the five studies was assessed according to the evaluation criteria established for assessing other circumcision method innovations:

- **Eligibility** – There were no exclusions to use of the vice clamp surgical assist device beyond those considered exclusions to circumcision by any method.
- **Efficacy** – 541 of 543 clients (99.6%) were successfully circumcised with the device alone. The two failures were due to operator error (neglected to fully tighten device, addressed by training and revised instructions for use) and mismatched parts (addressed by ensuring that all parts are presented in a single package).
- **Safety** – No severe AEs and 27 moderate AEs (5.0% [95% CI 3.3% to 7.2%]), which included moderate bleeding (13 cases, 2.4% [95% CI 1.3% to 4.1%]), haematoma (5 cases, 0.9% [95% CI 0.3% to 2.1%]) and infection (9 cases, 1.7% [95% CI 0.8% to 3.1%]). All bleeding cases occurred before discharge from the clinic after the procedure and were managed with sutures or pressure.
- **Pain** – Sufficient pain control was obtained with use of topical anaesthesia applied for at least 25 minutes before starting the procedure (topical pain control protocol used in all but the first study with 50 men [Unicirc Study 2], where injectable anaesthesia was used). The majority of clients experienced at most mild pain when the clamp was tightened to its maximum pressure.
- **Wound healing** – 264 of 279 clients followed to four weeks (94.6% [95 CI 91.3% to 97.0%]) were fully healed by four weeks after circumcision.
- **Cosmetic result** at four weeks:
  - 40 of 43 clients (93%) had a smooth, regular cosmetic result following Unicirc circumcision, compared with two of 21 clients (9%) following conventional surgical circumcision in the direct randomized comparison. The remaining clients had irregular or scalloped healing wounds.
  - Over all studies 273 of 277 clients (98.6% [95% CI 96.3% to 99.6%]) had a regular final cosmetic result following circumcision with the vice clamp surgical assist device. All other results – three irregular and one scalloped appearance – were associated with interventions to manage AEs and were expected to resolve spontaneously.
- **Other reported features** – very low blood loss, procedure duration about 10–15 minutes (approximately half the duration of conventional surgical circumcision), only a single visit required to complete the circumcision procedure.

Summary points and recommendations

Key points from the TAG discussion were:

- The main concern with the vice clamp surgical assist device was its effectiveness in preventing bleeding, particularly following an erection in the first few days after the procedure. The available results were reassuring, but the TAG considered continued surveillance of safety important as the device becomes more widely used.

- To date the device has been used by only a limited number of physicians, all of whom were experienced providers of conventional surgical circumcision and were assisted by nurses. It is important to collect more information on the safety of the device when used by mid-level providers in additional settings and to carefully follow all clients.
- The manufacturer had argued that the WHO Framework requirements of at least 1200 clients in four separate studies should be relaxed, as this device type is a surgical assist device. However, TAG members concluded there was no justification to modify the requirements and recommended that more information be systematically collected to establish safety in the hands of new providers including mid-level cadres, training requirements and standardization when following the instructions for use, including adhering to the minimum five minutes crush duration.
- While the device has been used successfully in adolescents, there is little information on whether topical anaesthesia provides sufficient pain control for younger adolescents with phimosis and/or penile adhesions. There are fewer concerns with the risk of bleeding complications in adolescents than in adults due to adolescents' less developed penile vasculature.

TAG members **recommended** that:

- the WHO Essential Medicines team evaluate the technical aspects of the device (specifications, manufacturing and quality control procedures) while further clinical data are systematically collected;
- opportunities be identified to support the additional field studies recommended above and to introduce the device to interested national voluntary medical male circumcision programmes, given its promising advantages over other circumcision methods.

Annex 1. Agenda

Time	Item	Lead
15:00 – 15:15	Opening Agenda and objectives, confidentiality agreements, declarations of interests	R Baggaley J Samuelson
15:15 – 16:15	PrePex elastic collar compression: efficacy, safety, acceptability • Evidence presentation on new data for clinical evaluation • Tetanus risk Discussion • Key questions: o Among adolescent boys and adult males seeking male circumcision (MC) for HIV prevention, is the PrePex (elastic collar compression) Day_0 foreskin removal procedure efficacious and safe as an additional MC method? o Is tetanus risk with this method similar to that of other methods that remove the foreskin at the time of procedure? o Is evidence sufficient? On haemostasis? o What additional evidence may be needed on both issues? • Advice to the Guideline Development Group and recommendation-making	Co-chair: T Hargreave T Farley L Thwaites
16.15 – 17:00	Unicirc surgical assist device: efficacy and safety • Evidence available Key discussion question: Are the clinical evaluation data sufficient and of adequate quality?	Co-chair: T Hargreave T Farley
	Closing and next steps	R Baggaley

Annex 2. List of participants

Members

Dr Tigistu Adamu Ashengo
Deputy Medical Director
Jhpiego
Washington, DC, United States of America

Professor Moses Galukande (Co-chair)
Associate Professor of Clinical Surgery
School of Medicine, College of Health Sciences
Makerere University
Kampala, Uganda

Dr Timothy Hargreave (Co-chair)
Urological surgeon
Edinburgh, United Kingdom

Professor Afua J. Hesse
Head, Department of Surgery
University of Ghana Medical School
Accra, Ghana

Mr Edgar Makona (unable to participate)
National Focal Point
Global Youth Coalition on HIV/AIDS
Nairobi, Kenya

Dr Owen Mugurungi (unable to participate)
Director, AIDS and TB
Ministry of Health and Child Welfare
Harare, Zimbabwe

Dr Pius Musau (unable to participate)
Consultant urologist/Senior Lecturer
Department of Surgery
Moi University, School of Medicine
Eldoret, Kenya

Mr William Potter
Stapleford Scientific Services
Cambridge, England
United Kingdom

Dr Christopher Samkange (unable to participate)
Director
Institute of Continuing Health Education
University of Zimbabwe, College of Health Sciences
Harare, Zimbabwe

Dr Ira Sharlip
Urological surgeon
Chair, American Urological Association Task Force on Male Circumcision
San Francisco, California, United States of America

Dr Helen Weiss
Reader in Epidemiology and International Health
London School of Hygiene and Tropical Medicine
London, United Kingdom

Technical expert

Dr C Louise Thwaites
Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam
Centre for Tropical Medicine and Global Health
University of Oxford
Oxford, United Kingdom

WHO secretariat

Dr Rachel Baggaley
Coordinator
Key Populations and Innovative Prevention
Department of HIV/AIDS

Ms Helena Ardura-Garcia

Technical officer
Department of Essential Health Technologies

Dr Timothy Farley
WHO consultant
Sigma3 Services SÀRL
Nyon, Switzerland

Ms Julia Samuelson
Nurse Epidemiologist

VMMC Focal Point
Key Populations and Innovative Prevention
Department of HIV/AIDS

Annex 3. Voluntary Medical Male Circumcision and Tetanus Risk – Final report by external consultant

Contents

Acronyms and abbreviations

TAG	Technical advisory group on innovations in male circumcision
WHO	World Health Organization
FRP	Foreskin removal procedure
MC	Male Circumcision
VMMC	Voluntary medical male circumcision
RCT	Randomized controlled trial
AE	Adverse event
SAE	Serious adverse event
IQR	Interquartile range
CI	Confidence interval
TTCV	Tetanus toxoid containing vaccine
DTP	Diphtheria Tetanus Pertussis
DTP3	3 doses Diphtheria Tetanus Pertussis

Background

Extensive evidence now exists indicating that male circumcision may reduce heterosexual transmission of HIV by approximately 60% [1–3]. Following the results of 3 large randomized controlled trials, in March 2007, WHO and Joint United Nations Program on HIV/AIDS (UNAIDS) issued recommendations that male circumcision be considered part of a comprehensive HIV prevention package in countries with generalized heterosexual epidemics. Modelling the impact of such scale up has indicated this would not only lead to lower HIV infection rates, but also result in long-term net savings to healthcare systems [4]. To date, over 18.6 million circumcision procedures have now been performed in males aged 10 years and older across 14 countries in eastern and southern Africa [5].

Initial studies of voluntary medical male circumcision (VMMC) were performed using conventional surgical circumcision techniques but increasing capacity to levels necessary for scale-up proved to be challenging and new methods of male circumcision were sought. Ideally these new methods would be safe, quicker and easier; facilitate more rapid healing or entail less risk of HIV transmission in the post-operative period; would be safe to use by healthcare providers with shorter periods of training and would be more cost-effective for scale-up than conventional methods. WHO developed a clinical evaluation research pathway to provide a consensus driven, systematic approach to the research required to assess efficacy and safety of a specific device [6]. The review of this evidence informs WHO guidance and the clinical performance component of the Prequalification Programme for Male Circumcision Devices [6]. WHO issued a conditional recommendation in 2013 on the use of prequalified devices. Two devices, an elastic collar compression device (PrePex™) and a collar-clamp device (ShangRing™) completed this prequalification programme in 2013 and 2015 respectively.

As part of ongoing safety review of the VMMC programmes, data on serious and moderate adverse events were required by WHO and the United States Presidents Emergency Plan for AIDS Relief (PEPFAR). By 2014, safety data identified 9 cases of tetanus, 6 of whom had died. In March 2015 WHO convened an informal meeting to assess tetanus risks associated with VMMC, reviewing the different modes of circumcision, pathogenesis and burden of tetanus infection, risk mitigation strategies and recognizing limited coverage of tetanus toxoid-containing vaccination (TTCV) in many areas [7]. Participants advised a dual approach to reducing the risk of tetanus, through rigorous surgical preparation for all procedures and good personal wound care education in addition to VMMC programmes phasing in contextually-relevant TTCV, with a minimum of a single dose at time of the circumcision procedure. Furthermore, post-market surveillance for all devices and safety monitoring for all circumcision methods should include reporting of serious adverse events (AEs) such as tetanus cases to the national programme, the manufacturer and WHO.

By May 2016, WHO had received reports of a total of 12 tetanus cases since active reporting began in 2014. Six of these cases occurred following conventional surgical circumcision and 6 following circumcision with elastic compression device. During the same period 3.04 million conventional surgical procedures had been performed and 90,500 procedures with the elastic compression device. The Technical Advisory Group on Innovations in Male Circumcision (TAG) discussed concerns over increased risk of tetanus in VMMC with the elastic compression device in July 2016, noting the difference in incidence rates and the biological plausibility of increased risk due to the persistence of necrotic tissue *in situ.* Following this discussion, the TAG recommended risk reduction measures by immunization with TTCV, prior to the use of this device method. A further expert discussion was held on August 12th 2016 when additional written and verbal submissions concerning the safety of male

circumcision were reviewed. After consideration of submissions, the TAG concluded that their advice of July 2016 was unchanged and that circumcision with a device method where the foreskin is left in situ and removed several days after application should be undertaken only if the client is adequately protected against tetanus by immunization with tetanus-toxoid-containing vaccine [8].

In previously unvaccinated individuals, VMMC with the elastic collar compression device requires 2 doses of TTCV at least 4 weeks apart and 6 weeks before device placement. This may lead to reduced uptake of VMMC and impede VMMC programme scale-up and acceptability. An adjusted method of application with foreskin removal procedure (FRP) shortly after device placement was therefore introduced (PrePex Day 0 FRP), aiming to reduce the amount of tissue left *in situ*. In a teleconference convened by TAG on May 2017, evidence regarding this adapted procedure was considered. Manufacturers submitted written documentation prior to the meeting and made oral submissions during the meeting. Interim data were presented from a study in Zambia where 500 men out of a projected sample size of 620 had completed 7-day follow-up [9]. In the initial phase of the protocol (119 clients) the procedure aimed to cut the foreskin immediately above the inner ring, but was subsequently modified to cutting along a line marked "just above the elastic ring" (381 clients). TAG considered that this adapted procedure was sufficiently different and that new clinical data submitted for must all refer to a common standardized procedure as defined in the WHO Framework on clinical evaluation [6,9].

In 2018 additional data were submitted by the manufacturer, namely: an updated report from the Zambia study, a revised standardized Day 0 FRP, two protocols for studies in Kenya and South Africa, and the proposed surgical backup facilities in case of complications or adverse events with the Day 0 FRP. After initial review of the evidence, further information was requested from the manufacturer on these study findings as follows. Firstly, a detailed report of the Zambia study was required, including a full account of the evolution of the PrePex Day 0 FRP, dates and reasons for modifications to the original protocol, exact number of clients in each site circumcised with each procedure, detailed description and analysis of adverse events, overall and in Lusaka and Livingstone separately. Secondly that the PrePex Day 0 FRP must be standardized so that all the minimum 1200 clients will have been circumcised using a common method. Thirdly, to reach the minimum of 1200 clients, additional clients could be added to planned studies in Kenya and South Africa but at least one more study site was required. A shortened follow-up period to at least 21 days from placement was however permissible for the additional clients over the proposed 100 in Kenya and 250 in South Africa, provided that at least half of the minimum 1200 clients had been followed to 49 days (7 weeks) from placement.

In considering tetanus risk, TAG concluded that 'the comparison with other circumcision methods (conventional surgery and ShangRing) was not strictly tenable since available clinical experience showed it was necessary to leave a cuff of foreskin distal to the device to prevent slippage and bleeding following foreskin removal'. The extent and configuration of the cuff needed clarification and data from a larger number of clients was needed to determine risks. The recommendation was therefore made that until the PrePex Day 0 FRP had been demonstrated to be safe and reproducible, clients in the new studies needed to be informed of the unknown risk of tetanus, and follow the same Day 7 foreskin removal TTCV advice [9].

Purpose of this report

WHO has requested further information from the studies, particularly to inform feasibility and importance of standardizing the amount of foreskin to retain and the risks of bleeding and displacement. Nevertheless, the magnitude of tetanus risk due to the cuff of tissue that remains with the device until final removal on Day 7 needs to be assessed.

The purpose of this report is to provide a background paper regarding use of the PrePex Day 0 foreskin removal procedure (FRP) method and tetanus risk. This involves evaluating the clinical evidence to clarify tetanus risk, the considerations and rationale on the level of tetanus risk associated with the PrePex Day 0 FRP, the conventional PrePex Day 7 FRP and conventional surgical methods, including evidence on anaerobic environment.

Tetanus acquisition and source of infection

Tetanus is a toxin-mediated disease caused by the bacterium *Clostridium tetani (C. tetani),* an anaerobic bacterium able to survive in the environment as resistant spores. Spores are able to germinate in anaerobic environments and during vegetative growth of the bacterium, tetanus toxin is produced. *C. tetani* spores are widespread within the environment and both humans and animals carry toxigenic *C. tetani* [10]. Neonatal tetanus is associated with traditional cord care practices such as using grass to cut the cord or applying dung, and it is assumed that these increase the risk of contamination of the umbilical stump with spores [11,12]. Evidence from case control studies in neonatal tetanus suggests that topical disinfectants can reduce the risk of tetanus acquisition [13].

C. tetani can be cultured from wounds of patients with tetanus, however in most cases there are either no obvious wounds (approximately 20-25%), or they are dry and associated with negative culture results[14–16]. In humans the incubation periods (the period from infection to the appearance of symptoms) are usually between 3 and 21 days, with median periods commonly reported between 6 and 12 days [14,17–19]. Unlike spores, the bacteria are highly sensitive to antibiotics although persistent cultures of *C. tetani* has been reported following antibiotic therapy, assumed to be due to poor tissue penetration of antibiotics [15].

Tetanus can be prevented by vaccination with tetanus toxoid containing vaccine, but a single dose is associated with little, if any, protection [20]. Although case reports exist in the literature, tetanus in the presence of protective antibodies is extremely rare [20]. Conversely infections of toxin-producing *C. tetani* can occur in immune individuals without symptoms or signs of tetanus [21].

Tetanus following circumcision

In non-immune individuals, there is a risk of tetanus following circumcision as a result of wound contamination by *C. tetani*. Contamination may occur during the procedure as a result of unclean practices, or due to wound contamination afterwards. *C. tetani* requires an anaerobic environment for vegetative growth and toxin production and therefore the risk of infection may depend on several factors. These include the time the wound is susceptible to contamination, patient or procedure-related practices that may increase or decrease the risk of contamination and the presence of a suitable anaerobic environment for bacterial germination and toxin production.

Types of Evidence necessary to quantify tetanus risk

Based upon known pathophysiology and epidemiology of tetanus described above, Table 1 summarises the types of evidence and likely sources of data required to quantify differential risk of tetanus acquisition according to method of circumcision.

Table 1: Summary of data required for assessment of risk of tetanus according to different procedures

Category	Data	Sources
Difference in tetanus incidence by circumcision method	Differences in tetanus incidence rates -number of tetanus cases by circumcision method and numbers of circumcision procedures according to method	Programme surveillance data National disease notifications Existing clinical trial adverse event data (field studies and randomized controlled trials)
Differences in immunity to tetanus where different circumcision methods have been used	Estimates of DTP vaccination coverage in target populations DTP3 data is likely to be more complete but DTP 4 and 5 data where possible Assumption: DTP3 coverage indicates possible immunity to tetanus and differences in coverage may indicate different risk of tetanus causing bias with incidence data.	Historical and national and local immunization coverage
	Serosurveillance studies of target populations	Published literature
Difference in risk of wound contamination post procedure	Differences in surgical wound with different circumcision procedures: Assumption: risk of contamination may vary depending on the type of wound healing, presence of foreign bodies and presence of necrotic tissue	Protocol/ standard operating procedures for different methods of circumcision
	Risk of unclean wound care post-procedure	Interviews with local healthcare workers/ programme operatives Adverse event data from clinical trials/ field studies

Category	Data	Sources
	Assumption: C. tetani contamination may occur due to poor hygiene post-procedure or the use of traditional remedies.	
	Differences in duration of healing Assumption: longer healing means higher risk of secondary contamination with C. tetani	Wound healing data for different circumcision methods from clinical trials/ field studies Expert opinion regarding healing process for different circumcision methods
	Differences in post-procedural wound care according to procedure method Assumption: Clean dressings are more likely to protect against contamination with C. tetani	Protocol/ standard operating procedures describing routine post-procedural dressing and wound care for different circumcision methods Published methodology of clinical trials Experience of programme providers
Differences in likelihood of spore germination and vegetative bacterial growth between different circumcision methods	Differences in microbiological environment between circumcision methods	Published literature regarding microbiological environment and circumcision Infection-related adverse event data from clinical studies
	Differences in residual amount of devitalized tissue depending on method of circumcision Assumption: devitalized tissue may be associated with increased risk of C. tetani spore germination and vegetative growth. Necrotic tissue may be indicated by presence of odour	Reports of odour following circumcision Protocol/ standard operating procedures for different circumcision methods Published methodology for clinical trials (RCTs and field studies) Experience of programme providers Photographic evidence from clinical trials Information from programme providers

Available evidence

Methodology and documents reviewed

To gather available evidence WHO, relevant experts and study principal investigators were approached. In addition to programme providers and stakeholders, two specific experts with considerable experience in tetanus were consulted: one infectious disease/ critical care specialist with extensive experience in research and clinical management of tetanus (> 5000 cases) and one a clinical microbiologist with specific clinical tetanus and *C. tetani* experience.

Relevant TAG reports were reviewed and a Pubmed literature search was conducted using terms "Circumcision" AND "HIV"; "Shang Ring", "PrePex".

A list of documents reviewed is attached in Appendix 1.

Cohort studies were evaluated according to STROBE statement for STrengthening the Reporting of Observational studies in Epidemiology [22]. Randomized controlled trials were evaluated according to the Consort statement [23]. In addition, studies were analysed with particular reference to risk of tetanus. The following features were extracted from reports.

1. Incidence of adverse events (AEs) and serious adverse events (SAEs), including period patients were actively followed up for these.
2. Wound healing rates and time course thereof
3. Odour or wound infection
4. Vaccination protocol applied to study subjects
5. Compliance of evidence with TAG specifications as report May 2017

Evidence certainty was summarized according to WHO guidelines. Very low certainty was attributed when only low- quality studies or expert opinion was available whereas high certainty was attributed to several high-quality randomized trials or meta-analyses.

Tetanus incidence

Number of tetanus cases reported in the VMMC programme

Up to April 2018 a total of 18 cases of tetanus within the VMMC programme have been reported to WHO. Of 15 cases, previously assessed to have a probable causal association with circumcision, 10 (67%) have died [8].

Table 2: VMMC cases of tetanus reported to WHO up to April 2018

Year	Number of tetanus cases (number of deaths)			
	Surgical	ShangRing	PrePex Day 7 FRP	PrePex Day 0 FRP
2012	2 (1)	0	-	-
2013	1* (0)	0	-	-
2014	3 (3)	0	3 (2)	-
2015	3 (2)	0	1 (0)	-
2016	0	0	3 (3)	-
2017	0	0	1 (0)	1 (0)**

*Probable causal relationship with circumcision not established

** See below

The majority of surgical cases carried out before 2014 have not been subject to active surveillance. However, since 2014, all countries have been requested to report all deaths and inpatient hospitalizations occurring within 30 days of any circumcision method as part of ongoing safety surveillance of the VMMC program[7]mes.

No data are available on loss-to follow up before the end of active surveillance except for those of clinical studies. In studies of PrePex Day 0 FRP, follow-up rates at day 42-49 were high (≥88%) [24–26]. Similarly in studies of PrePex Day 7 FRP loss to follow-up was low [27–31], except one study where approximately 50% did not return for the day 49 follow-up visit [32]. Published literature regarding ShangRing circumcision also shows high rates of follow-up (most studies report > 90% at 4- 6 weeks post device placement [33–37].

More than 2,500 cases of circumcision using the PrePex Day 7 FRP method have completed active surveillance as part of the clinical evaluation process after prequalification granted.

Similar data on the number of ShangRing procedures is awaited.

Eight cases of tetanus have been reported between 2012 and 2014 following conventional surgical-method circumcision and eight following PrePex Day7 FRP (Table 2). One case of mild tetanus presenting 22 days after PrePex Day 0 FRP was reported to WHO [25]. As a mild case of tetanus, there is some uncertainty in diagnosis, however of note the diagnosis of tetanus was made by the two physicians who actually saw and examined the patient and the senior physician making the diagnosis was experienced in tetanus. An independent expert, consulted in this document agrees that tetanus cannot be excluded (Appendix 2). In expert opinions and manufacturer's conclusions presented in the study final report about this event there are some errors/inconsistencies which are addressed in Appendix 2 [25].

Currently this case is included here as it meets the criteria for being consistent with causal association, i.e. there being signs and symptoms of tetanus within a plausible incubation period with a reportedly normal healing wound and no alternative tetanus entry points evident elsewhere on body [7].

Number of circumcision procedures performed within VMMC programme

18.6 million circumcision procedures have been performed between 2008 and 2017, the majority of these have been performed by surgical methods [5]. 1,626 procedures with the PrePex Day 0 FRP have been performed [24–26,38].

Data are currently awaited for the total number of procedures with Shang Ring, PrePex Day 7 and surgical (dorsal slit and forceps guided) methods.

Anecdotally 3 cases occurred in Uganda in 2018, however, direct reports have not been received by WHO on these cases.

Calculated incidence rates according to procedure type

At TAG review in June 2016 data from Rwanda, Uganda, Tanzania and Kenya was considered. For the years 2014-2016, a total of 113,662 circumcisions were performed using PrePex Day 7 FRP method, amongst these 6 cases of tetanus occurred giving an incidence of 5.28 (95% CI 1.94-11.5) per 100,000 procedures performed. During the same period 3,717,338 surgical procedures were carried out, amongst which 6 cases of tetanus occurred, giving an incidence of 0.161 (95% CI 0.059 -0.351) per 100,000 procedures. When data from just Rwanda and Uganda was examined (the only places where tetanus occurred), similar incidence figures of 5.45 (95% CI 1.99-11.8) and 0.151 (95% CI 0.031- 0.441) were calculated for PrePex and surgical methods respectively [8].

To date, a total of 1,626 clients have undergone circumcision using the PrePex Day 0 FRP method. The majority (1,507 clients) received the modified procedure (Phase 2 of the Zambian field study [24]). Following PrePex Day 0 FRP, tetanus in the population at risk (ie those not given 2 doses of TTCV prior to the procedure) was calculated to be 1 case in 1,116 patients, corresponding to incidence of 90 per 100,000 (95% CI 2.3 - 500).

No cases of tetanus have been reported to WHO following ShangRing procedure.

Differences in immunity to tetanus

Number of those at risk of tetanus within the VMMC programme.

All unvaccinated or incompletely vaccinated clients within VMMC programmes may be at risk of tetanus. In July 2016 TAG issued new guidance that PrePex Day 7 procedures should only be carried out following 2 doses of TTCV. Of note, 3 of the cases of tetanus following circumcision with PrePex method occurred after this date in individuals not vaccinated with 2 doses of TTCV. One case was reported to be unvaccinated. Two cases were given one dose of TTCV at device placement, one of whom received PrePex Day 0 FRP where a one-dose schedule was specified in the trial protocol [25].

Of the 1,626 clients undergoing PrePex Day 0 FRP circumcision, 510 received the recommended 2 doses of TTCV before device placement [38].

To estimate the proportion of the population likely to be unvaccinated, Dalal *et al* reviewed vaccination coverage of primary diphtheria, tetanus pertussis (DTP3) immunization from WHO and United Nations Children's Fund data from 1980-2013 [39]. During this period, coverage in the WHO African region increased from <20% in 1980 to 75% in 2013. Specific evaluation was made in the 9 countries implementing the VMMC programme which had either reported a tetanus case or had ≤75% coverage for at least 2 years since 2000. In these countries DTP3 coverage was an average 80% in 2005

and between 65% and 98% in 2013. No data were available on 4th,5th or 6th booster doses necessary for long-term immunity.

Sero-surveillance data from community surveys in Kenya, Tanzania and Mozambique from 2012-2013 indicates that tetanus seroprotection was reduced in older children compared to those < 4 years old in 2 of 3 studied countries, suggesting lack of 4th and 5th TTCV boosters. Furthermore there were significant differences between males and females in individuals > 15 years old in all 3 countries [40].

Possible DTP3 coverage of subjects recruited in studies of PrePex Day 0 FRP studies estimated using United Nations Children's Fund national DTP3 data is shown below in Table 3. All studies included birth cohorts born in years before data are available and coverage in these age-groups is assumed to be lower than the earliest reported data. Specific coverage data for the years 1984-1985 in Kenya, the birth year of the tetanus case following Day 0 FRP discussed above, are 58% and 72% respectively.

Table 3: Estimated tetanus protection in subjects in PrePex Day 0 FRP studies

Study	Study TTCV procedure	Age of subjects recruited in study	DTP3 coverage in country of study
Rwanda [38] **(n=51)**	2 doses TTCV prior to device placement	Mean 21.3 years (birth year 1996) 65% born 1968-2000	17% in 1981 (earliest available data) 90% in 2000
Zambia [24] **(n=500)**	'followed the Zambia tetanus vaccination guidelines for surgical circumcision that does not include tetanus vaccine'	Mean 22.7 years (birth year 1995) 95% born 1968-2000	49% in 1983 (earliest available data) 85% in 2000
Kenya Field Study [25] **(n=515)**	1 dose TTCV on day of device placement	Median 28 years (birth year 1989) 77% born 1978 – 2000	58% in 1983 (earliest available data) 82% in 2000
Kenya RCT [26] **(Day 0 n = 101)**	1 dose of TTCV on day of device placement for Day 0 FRP; 2 doses prior to placement for Day 7 FRP.	Mean 31.4 years (birth year 1986) >99% born 1968-2000	58% in 1983 (earliest available data) 82% in 2000

Possible protective immune response to single dose TTCV

There are limited data on the efficacy of a single TTCV dose in vaccine-naive populations. Evidence surrounding protection conferred by a single TTCV in the context of the VMMC programme was carefully examined at the informal consultation in 2015 where experts concluded that a single TTCV dose in an individual who has never received any vaccination (vaccine-naïve) is inadequate [7].

Antibody response to booster vaccination in populations who have received primary DTP3 indicates antibody responses may be elicited many years later however the kinetics and magnitude of this are variable. In Indian junior medical staff who reported receiving primary DTP3 immunization, a single dose of 5 Lf TTCV produced 4-fold rise in antibody titres measured by mouse neutralization assay in 26/30 individuals at 1 month and a 10-fold rise in the remaining 4/30 individuals. Despite this, 50% showed antibody titres <0.01 IU/ml [41]. In Spanish 18-30 year-olds, assumed to have received primary DTP3 vaccination, protection rose from 90% to 99.5% 1 month after a single booster of TTCV [42].

Expert consideration of evidence surrounding TTCV boosters in the VMMC programme in 2015 concluded that a booster dose should be given ideally 14 days, and at least 7 days prior to the procedure based on evidence that it takes 6 or 7 days for a significant antibody response following booster immunization and that antibodies continue to rise until about 14 days [7]. A further update on tetanus immunity following TTCV was published by WHO in 2018, stating that evidence regarding the kinetics of the immune response to a booster dose administered more than 10 years following an infant schedule is currently lacking [20]. Thus it remains unknown how rapidly antibody titres may rise in this population, especially given uncertainty about DTP 4th and 5th immunizations.

Other indicators of likely population immunity

Knowledge of overall background incidence of tetanus in communities targeted by the VMMC allows an estimate of population immunity to tetanus and may also allow comparison of incidence rates within the programme. However, due to paucity of national reporting of non-neonatal tetanus cases in countries within the VMMC programme, estimating background incidence of tetanus is challenging. Published literature, however, indicates that tetanus remains a significant problem in men in these countries [43]. Dalal *et al* identified 32 studies in sub-Saharan Africa between 2003 and 2014, reporting total of 6,582 inpatient cases of non-neonatal tetanus [39]. The majority of these cases were males and median case-fatality rate was 44%. In a study examining male non-neonatal tetanus admissions to a single centre in Tanzania from 2008 – July 2016, medical notes were available in 162 cases, revealing 6 cases where there was a history of recent circumcision but no other obvious wound. Five or these cases had been circumcised outside the VMMC programme. The case within the VMMC programme had limited data about procedure or post-procedural care but was known to have HIV. Time from circumcision to first symptom for all 6 cases was between 1 and 2 weeks [44].

Nanteza *et al* accessed Ugandan National District Health Information Software-2 database for tetanus cases between 2012–2014, identifying a total of 1,311 outpatient cases in males above 5 years-of-age occurring in 2014 [45]. Inpatient data from the same database were extracted by WHO and used to estimate annual male inpatient incidence of tetanus at 3 cases per 100,000 population, or 0.25 cases per 100,000 months [8].

Difference in risk of wound contamination post-procedure.

Differences in surgical wound with different circumcision procedures

Surgical circumcision methods involve direct wound closure with sutures and healing of the wound by primary intention. Both collar-clamp and elastic compression device methods of circumcision involve healing by secondary intention. In PrePex Day 0 FRP method circumcision and ShangRing circumcision, the cut is distal to the devitalized tissue shortly after device placement, whereas with PrePex Day 7 FRP method no cut is made until device removal. In other surgical situations, secondary intention

healing may be associated with longer healing times and possible increased risk in surgical site infection [46].

With both collar-clamp and elastic-ring compression devices, haemostasis results from compression of the foreskin by the device. Differing degrees of compression may occur between the two devices as indicated by differences in adverse event profiles. Bleeding may be a particular problem in the PrePex Day 0 FRP circumcision method and prompted the revision of the procedure to leave a small amount of tissue distal to the ring [24]. A comprehensive report of adverse events of all procedures is currently in preparation for TAG review. However, published studies of ShangRing in African adults, report 5 bleeding events in recorded in 3,044 device placements [33–36,47–50]. In studies of PrePex Day 0 FRP, 15 moderate or severe adverse events associated with bleeding occurred within 7 days of device placement from a total of 1,626 device placements (Table 3). Six of these cases occurred with the original Day 0 FRP (119 patients), after which the FRP was modified to include a more distal cutting line [24].

The modified PrePex Day 0 FRP protocols instruct foreskin cutting along a marked line. These have been reported as "just above the inner ring on the dorsal side but leaving a bit of skin on the ventral side where the frenulum is located" [24,26,38] or "2-3 mm above the inner ring. At the frenulum area, the line was marked approximately 5mm above" [25]. Providers have reported that this modified procedure is simple to perform and that quality-control regarding of the amount of residual foreskin is possible using photographs taken after the procedure.

No data were found describing residual tissue following ShangRing procedure but photographs and training information have shown very minimal residual tissue (<1mm) [51].

Differences in duration of healing

In most comparative studies of circumcision methods within the VMMC programme, data suggest that healing is faster in circumcision following conventional surgery compared to device-related methods [27,31,34–36].

Differences in interpretation of wound-healing criteria means that there are wide variations in reported mean and median healing times between studies. For ShangRing these range from 14 -43 days [34,36]. Following PrePex Day 7 FRP circumcision , healing times of 21-33 days are noted [27,52,53]. Trial protocols of PrePex Day 0 FRP studies did not allow exact quantification of healing times, but more than 90% clients are reported to be fully healed at end of follow up and similar healing rates were reported in Day 7 and Day 0 FRP groups [26].

Thus although it is likely that surgical wounds heal faster than those related to device-methods, healing times are similar between all device methods.

Differences in standard wound care according to procedure method

Standard wound-care may vary between circumcision methods affecting the risk of contamination with *C. tetani*. Personal communications have indicated these practices may be variable between methods and centres. WHO/ UNAIDS guidance acknowledges adult male circumcision is more complex than in infants and states "Adult circumcision requires suturing and dressing, and once bleeding has ceased the wound is dressed and the dressing is left in place for 24–48 hours" [54].

Few clinical studies concerning circumcision within the VMMC programme have given clear details about post-procedural wound care, except for PrePex Day 0 and Day 7 FRP protocols where there are

instructions regarding dressings to be applied after device removal (at day 7). It is unclear whether in practice, dressings are applied at the time of foreskin excision with ShangRing, PrePex Day 0 FRP or surgical methods.

Traditional wound-care practices are common in many areas targeted by the VMMC and are likely to increase tetanus risk[55,56] . A report to WHO (April 2012 – March 2016) noted that 5 out of 13 cases had applied a home remedy [39,57]. Clinical studies have also reported providers observations that some clients had difficulties with hygiene or applied traditional poultices [30]. Forgetting, disregarding or misinterpreting provider instructions about post-procedural wound care has also been highlighted, particularly amongst adolescents [58].

Differences in likelihood of spore germination and vegetative bacterial growth between different circumcision methods

Differences in microbiological environment between circumcision methods

The microbiological environment before and after surgical circumcision was studied using paired pre- and post-circumcision swab samples from 12 HIV-negative participants during a randomized trial of male circumcision for HIV prevention in Uganda. These samples, taken from the coronal sulcus before and after surgical circumcision (sleeve procedure method) showed a significant reduction in anaerobic bacteria [59]. In a case-control study with samples from the same clinical trial, circumcised men had reduced bacterial load, particularly anaerobic bacteria, compared to uncircumcised controls 1 year post-circumcision, [60]. Furthermore the anaerobic load was associated with HIV transmission risk [61].

One study specifically examining the PrePex Day 7 FRP circumcision method, analyzed the subpreputial microbiome in 2 men circumcised with this method [62]. Swabs were taken on day 7 and compared with those of 145 uncircumcised men (historic controls in previous studies above). Increased bacterial load was seen in PrePex users, largely due to increased anaerobic bacteria.

There are no data on anaerobic environment after PrePex Day 0 FRP or Shang Ring procedures.

A telephone conference to discuss microbiological aspects of tetanus risk with particular reference to PrePex Day 0 FRP was conducted with a clinical microbiologist with extensive experience in tetanus who concluded that it seems logical that reducing the amount of residual foreskin present in the week following placement of the PrePex will decrease the chance of an anaerobic environment, suitable for *C. tetani*, developing under the foreskin. Furthermore, mitigation of tetanus risk may be by provided by ensuring as clean an environment as possible around the wound after circumcision – for example providing sterile saline for washing, chlorhexidine dressing.

Odour

Odour has been noted to occur following PrePex method circumcision and previous TAG discussion has considered whether this may indicate tissue necrosis or anaerobic activity [63]. Gas production and associated fetid odour are also reported when *C. tetani* is grown in the laboratory [7]. A randomized controlled trial in Rwanda evaluated different post-procedural wound care regimes following PrePex Day 7 FRP with regard to odour (assessed subjectively and objectively with a Nasal Ranger) and found that daily chlorhexidine almost completely eliminated odour [64].

In studies of PrePex Day 0 FRP, odour was assessed at telephone follow-up 3 days after device placement in all studies, and at day 7 visit in one study. Difficulty contacting subjects by telephone was noted and telephone follow up rates were lower than follow up clinic visits. In the Zambia, 72/422 (17%) clients contacted at day 3 noted weak odour [24]. In Rwanda 18 of the 299 (6%) clients contacted by telephone on day 3 post placement reported odour [38]. In the Kenyan randomized controlled trial at day 3 post placement, 0/88 (0%) undergoing Day 0 FRP noted odour compared to 1/8 (13%) undergoing Day 7 FRP [26]. At day 7, 3/101 (3%) in the Day 0 FRP group reported odour compared to 18/42 (43%) in the Day 7 FRP group. Providers in Rwanda and Zambia reported improvement or absence of odour at the day 7 removal visit. In Kenya, 10 (2.6%) of clients reported odour whist wearing the device, but at day 14 after device placement, 15.2% clients reported odour from slough in the wound area as a concern [25].

No data were found regarding odour and other methods of circumcision.

In the teleconference with clinical microbiologist described above, the issue of odour was discussed. It was noted that, when considering odour, odour is not exclusively indicative of anaerobic infection and other pathogens such as Staphylococcus aureus infections can produce odour when causing infection.

Wound infections

Adverse event data may also indicate differing risk of tetanus infection with different methods. In Published literature concerning African adults with ShangRing placements, out of 3,044 device placements 28 infections were reported. Twenty-four of these infections were graded as mild and came from a single study [36]. The remaining 3 infections were graded as moderate. In studies of PrePex Day 0 FRP (1,626 device placements), a total of 2 infection-related moderate/severe events have been reported, with one possible mild infection also noted (Tables 4 & 5). For PrePex Day 7 FRP, 23 infection-related adverse events were reported from a total of 8,868 device placements. More complete data is expected in the full adverse event report currently in preparation for TAG review, however it does not appear that PrePex Day 0 circumcision is associated with increased risk of wound infection.

Table 4. Adverse events and serious adverse events at day 7 after device placement

Study location	Event	Grade	Action
Zambia Phase 1[24]	Bleeding the evening after foreskin removal and swelling at frenulum	Severe	Bleeding the previous evening after foreskin removal and swelling at the frenulum
Zambia Phase 1	Bleeding post foreskin removal	Severe	Pressure applied but was not effective. Device removed and sutures applied
Zambia Phase 1	Bleeding post foreskin removal	Moderate	Pressure and vitamin K injection
Zambia Phase 1	Generalized oedema and haematoma	Moderate	Compression to remove all clots no active bleeding detected, Ibuprofen tablets given for the oedema.
Zambia Phase 1	Bleeding post foreskin removal	Mild	Pressure and dressing
Zambia Phase 1	Bleeding post foreskin removal	Severe	Pressure applied but was not effective. Device removed and sutures applied
Zambia Phase 1	Bleeding from the frenulum post foreskin removal	Severe	Pressure applied but was not effective. Device removed and sutures applied
Zambia Phase 2[49]	Bleeding post foreskin removal	Moderate	Pressure
Zambia Phase 2	Bleeding from the frenulum post foreskin removal	Severe	Pressure applied but was not effective. Device removed and sutures applied
Zambia Phase 2	Wound infection	Moderate	Area clean and oral antibiotics administrated
Rwanda[38]	hematoma and bleeding several hours after device placement	Moderate	Device removed and SMC performed
Rwanda	Bleeding several hours after device placement	Moderate	Device removed and SMC performed
Rwanda	Bleeding 10 minutes following FRP	Moderate	Device removed and SMC performed
Rwanda	Bleeding immediately following FRP	Moderate	Device was removed, inner foreskin was trimmed and sutures applied.
Kenya Field Study[25]	Self-removal and mild bleeding 2 days after device placement	Moderate	Device removed and wound sutured.
Kenya Field Study	Self-removal 2 days after placement (no bleeding)	Moderate	Wound sutured.
Kenya Field Study	Device displacement and bleeding	Moderate	Wound sutured

Kenya RCT Day 0 FRP[26]	Bleeding after FRP	Moderate	Wound sutured, device left in place for day 7 removal

Table 5: Adverse events occurring after 7 days

Study location	Event	Grade	Action
Kenya RCT Day 7 FRP	Bleeding day 20 patient trying to remove slough	Moderate	Wound sutured
Kenya RCT Day 0 FRP	Mild infection shaft of penis at day 49 visit	Mild	Antibiotics 1 week
Kenya Field Study	Mild tetanus day 22 visit	Serious	Hospital admission
Rwanda	Bleeding and fever reported at day 21 telephone follow up	Mild	Client did not attend nor respond to contact. All normal at day 49 visit

Summary of evidence

Cases of tetanus have been reported following both conventional surgical circumcision and PrePex methods. When frequency of device placement is considered, incidence of tetanus following PrePex Day 7 FRP is elevated compared to other methods of circumcision. One case of mild tetanus has been reported following PrePex Day 0 FRP. To date, however, this is an isolated case and confidence intervals for this estimate are very wide and there will always remain some uncertainty about the diagnosis. *There is very low level certainty evidence indicating that tetanus incidence is increased following PrePex Day 0 FRP circumcision.*

A significant proportion of clients in VMMC programmes are likely not to have received primary DTP3 immunization against tetanus based on WHO reported data. Lack of data on 4th, 5th and 6th doses of TTCV (ie. vaccination beyond infancy) means it is unclear whether even those who have received primary DTP3 vaccination will have received booster doses necessary for on long-term immunity. Lack of immunity in these populations is supported by clinical case series data indicating that non-neonatal tetanus continues to occur in countries where the VMMC is implemented and sero-surveillance studies. Whilst individuals who have completed DTP3 immunization may respond to a single booster TTCV, adequate antibody protection may not occur until at least 7 days following immunization. *There is moderate certainty about evidence indicating that a substantial proportion of target VMMC population will lack immunity to tetanus.*

Considering the surgical procedures themselves, there are some specific differences that may affect tetanus risk. The modified PrePex Day 0 FRP requires cutting along a more distal excision line than originally proposed, leaving up to 5mm residual tissue. Whilst there is evidence to suggest that PrePex Day 7 FRP procedures are associated with increased anaerobic growth in a small number of patients studied, *there are no specific data and therefore no evidence concerning PrePex Day 0 FRP*. *There is moderate certainty evidence that clinical surgical site infections requiring antibiotic treatment are not increased following PrePex circumcision compared to other methods of circumcision.*

Reports of odour with PrePex Day 0 FRP appear lower than those with Day 7 procedures, but nevertheless remain and persist after device removal in some individuals (*moderate certainty evidence*).

Wound healing rates between different device-methods of circumcision appear similar, but are prolonged compared to surgical circumcision (*moderate certainty evidence*). This may be increase the length of time of vulnerability to *C. tetani* wound contamination, but there does not appear to be a difference in healing times between different device-associated methods (*moderate certainty evidence*).

It is unclear from available data how post-procedural wound care varies between circumcision methods. At least in some cases, PrePex Day 0 FRP circumcision wounds are not dressed after device placement. Dressing the wound may reduce the risk of *C. tetani* contamination (*very low certainty evidence)*. Traditional remedies and applications also pose an increased risk of contamination and provider instructions are not always followed (*high certainty evidence*) but there is no evidence available to assess whether the application of traditional remedies differs between circumcision procedures.

Conclusions

Based on current available evidence it is difficult to quantify exact risk of tetanus. However

1. One possible case of tetanus has been reported shortly after a circumcision procedure, but uncertainty about the diagnosis prevents definite conclusions about increased risk.
2. VMMC programmes are likely to be operating in communities were a significant proportion of males are at risk of tetanus due to lack of serological protection.
3. The modified PrePex Day 0 FRP is associated with a residual ring of at least 2-3 mm necrotic tissue. This may be a source of increased anaerobic presence.

Further Evidence

Any unvaccinated individual sustaining a wound is at risk of tetanus. Risk may be increased if the wound is contaminated or if a suitable anaerobic environment exists for *C tetani* germination. Quantification of tetanus risk following PrePex Day 0 FRP remains difficult due to uncertainty about tetanus incidence following the procedure and lack of specific knowledge about the anaerobic environment after Day 0 FRP compared to other methods of circumcision.

Feasibility of gathering further evidence

Whilst further surveillance data would increase certainty about tetanus incidence following VMMC, given rarity of events the sample size required to provide a reliable estimate of risk is likely to be unfeasible a high-quality follow up is required to ensure complete and reliable data. Furthermore, whilst 3 previous studies have not fully vaccinated individuals against tetanus prior to circumcision PrePex Day 0 FRP, careful consideration should be given to the ethical implications of advocating this approach in further studies.

Further data concerning the subpreputial microbiome following different circumcision methods may allow comparison of anaerobic load between different methods. Whilst this data may be of some value, interpretation is limited by lack of knowledge about the exact environmental requirements for *C tetani* growth *in vivo* and may rely on untested assumptions that risk of tetanus is proportional to anaerobic load.

References

1. Bailey RC, Moses S, Parker CB, et al. Male circumcision for HIV prevention in young men in Kisumu , Kenya : a randomised controlled trial. *Lancet*. 2007;369:643-656.
2. Auvert B, Auvert B, Taljaard D, et al. Randomized , Controlled Intervention Trial of Male Circumcision for Reduction of HIV Infection Risk : The ANRS 1265 Trial. *PLoS Med*. 2005;2(11):e298.
3. Gray RH, Kigozi G, Serwadda D, et al. Male circumcision for HIV prevention in men in Rakai , Uganda : a randomised trial. *Lancet*. 2007;369:657-666.
4. Njeuhmeli E, Forsythe S, Reed J, et al. Voluntary Medical Male Circumcision : Modeling the Impact and Cost of Expanding Male Circumcision for HIV Prevention in Eastern and Southern Africa. *PLoS Med*. 2011;8(11).
5. WHO Progress Brief Voluntary Medical Male Circumcision for Hiv Prevention Key Highlights on the Progress of Voluntary Medical Male Circumcision (VMMC) for HIV Prevention. 2018.
6. World Health Organization (WHO). Framework for Clinical Evaluation of Devices for Male Circumcision. 2012.
7. World Health Organization (WHO). *WHO Informal Consultation on Tetanus and Voluntary Medical Male Circumcision: Report of Meeting Convened in Geneva, Switzerland, 9-10 March 2015.*; 2015.
8. World Health Organization. Tetanus and Voluntary Medical Male Circumcision: risk according to circumcision method and risk mitigation Report of the WHO Technical Advisory Group on Innovations in Male Circumcision - consultative review of additional information 12 August 2016. *World Heal Organ*. 2016;(August). http://apps.who.int/iris/bitstream/10665/250146/1/WHO-HIV-2016.19-eng.pdf?ua=1.
9. WHO Technical Advisory Group on Innovations in Male Circumcision: Evaluation of Two Adult Devices. *Report of Teleconference 17 May 2017.*; 2017. http://www.shangring.cn/downloadcenter/WHO_TAG_on_Innovations_in_male_circumcision_Meeting_Report_Evaluation_of_Two_Adult_Devices_January_2013.pdf.
10. Wilkins CA, Richter MB, Bergh N, et al. tetani Occurrence of Clostridium soil and horses. *S Afr Med J*. 1988;73:1987-1989.
11. Aqeel AY, Arishi HM, Ageel HI, Arishi NH. Epidemiological and clinical aspects of neonatal tetanus from a tertiary care hospital. *Int J Pediatr Adolesc Med*. 2017;4(2):71-74.
12. Raza S a, Avan BI. Disposable clean delivery kits and prevention of neonatal tetanus in the presence of skilled birth attendants. *Int J Gynaecol Obstet*. 2013;120(2):148-151.
13. Parashar U, Bennett J, Boring J, Hlady W. Topical antimicrobials applied to the umbilical cord stump: a new intervention against neonatal tetanus. *Int J Epidemiol*. 1998;27(5):904-908.
14. Thwaites CL, Yen LM, Nga NTN, et al. Impact of improved vaccination programme and intensive care facilities on incidence and outcome of tetanus in southern Vietnam, 1993-2002. *Trans R Soc Trop Med Hyg*. 2004;98(11):671-677.
15. Campbell JI, Lam TMY, Huynh TL, et al. Microbiologic characterization and antimicrobial susceptibility of Clostridium tetani isolated from wounds of patients with clinically diagnosed tetanus. *Am J Trop Med Hyg*. 2009;80(5):827-831.
16. Hanif H, Anjum A, Ali N, et al. Isolation and antibiogram of clostridium tetani from clinically diagnosed tetanus patients. *Am J Trop Med Hyg*. 2015;93(4):752-756.
17. Chalya PL, Mabula JB, Dass RM, Mbelenge N, Mshana SE, Gilyoma JM. Ten-year experiences

with Tetanus at a Tertiary hospital in Northwestern Tanzania: A retrospective review of 102 cases. *World J Emerg Surgf*. 2011;6(1):20.

18. Mahieu R, Reydel T, Maamar A, et al. Admission of tetanus patients to the ICU: a retrospective multicentre study. *Ann Intensive Care*. 2017;7(1).
19. Roper M, Wassilak S, Tiwari T, Orenstein W. Tetanus toxoid. In: Plotkin S, Orenstein W, Offit P, eds. *Vaccines*. Elsevier Inc; 2013:746-772.
20. Basta N, Borrow R, Miller E. *WHO Immunological Basis for Immunization Series Module 3 Tetanus Update 2018*.; 2018.
21. Fournier P, Levy P, Million M, Croce O. Genome of a chronic osteitis-causing Clostridium tetani. 2014:2-3.
22. STROBE Statement: STrengthening the Reporting of OBservational studies in Epidemiology. https://www.strobe-statement.org/index.php?id=available-checklists.
23. Consort Consolidated Standards of Reporting Trials. consort-statement.org.
24. Linyama D. *Safety and Acceptability Study of Non-Surgical Male Circumcision Device for Adult and Adolescent Male Population When Removing the Foreskin Shortly after Placement of PrePex Device Performed at Lusaka and Livingstone, Zambia*.; 2018.
25. Agot K. *A Safety and Acceptability Study of PrePex™ Circumcision Device among Adolescent Boys and Adult Men When Foreskin Is Removed Shortly after Device Placement [Day0 Foreskin Removal Procedure*.; 2018.
26. Otieno F. *A Prospective, Randomized, Open Label Trial Comparing PrePex™ Day7 Foreskin Removal Procedure (FRP) to a PrePex Day0 FRP of Male Circumcision in Resource Limited Settings*.; 2017.
27. Mutabazi V, Kaplan SA, Rwamasirabo E, et al. HIV prevention: Male circumcision comparison between a nonsurgical device to a surgical technique in resource-limited settings: A prospective, randomized, nonmasked trial. *J Acquir Immune Defic Syndr*. 2012;61(1):49-55.
28. Feldblum P, Martinson N, Bvulani B, et al. Safety and Efficacy of the PrePex Male Circumcision Device. *JAIDS J Acquir Immune Defic Syndr*. 2016;72:S43-S48.
29. Tshimanga M, Hatzold K, Mugurungi O, et al. Safety profile of prepex male circumcision device and client satisfaction with adolescent males aged 13-17 years in Zimbabwe. *J Acquir Immune Defic Syndr*. 2016;72:S36-S42.
30. Kohler PK, Barr BAT, Kangombe A, et al. Safety, feasibility, and acceptability of the prepex device for adult male circumcision in Malawi. *J Acquir Immune Defic Syndr*. 2016;72:S49-S55.
31. Kigozi G, Musoke R, Watya S, et al. The safety and acceptance of the PrePex device for non-surgical adult male circumcision in Rakai, Uganda. A non-randomized observational study. *PLoS One*. 2014;9(8).
32. Mavhu W, Hatzold K, Ncube G, et al. Safety and acceptability of the PrePex device when used in routine male circumcision service delivery during active surveillance in Zimbabwe. *J Acquir Immune Defic Syndr*. 2016;72:S63-S68.
33. Barone MA, Awori QD, Li PS, et al. Randomized trial of the Shang Ring for adult male circumcision with removal at one to three weeks: Delayed removal leads to detachment. *J Acquir Immune Defic Syndr*. 2012;60(3):82-89.
34. Sokal DC, Li PS, Zulu R, et al. Randomized Controlled Trial of the Shang Ring Versus Conventional Surgical Techniques for Adult Male Circumcision. *JAIDS J Acquir Immune Defic Syndr*. 2014;65(4):447-455.

35. Kigozi G, Musoke R, Watya S, et al. The acceptability and safety of the Shang Ring for adult male circumcision in Rakai, Uganda. *J Acquir Immune Defic Syndr*. 2013;63(5):617-621.

36. Kanyago S, Riding DM, Mutakooha E, Lopez De La O A, Siedner MJ. Shang ring versus forceps-guided adult male circumcision: A randomized, controlled effectiveness study in Southwestern Uganda. *J Acquir Immune Defic Syndr*. 2013;64(2):130-133.

37. Feldblum, P Mwambula C, Selemani M, Long S, et al. Prospective Observational Study of the ShangRing Device for Adult Medical Male Circumcision in a Routine Clinical Setting in Malawi. *Afr J Reprod Med*. 2016;20(4):60-66.

38. Bitega JP, Ngeruka M. *Safety and Acceptability Study of Non-Surgical Male Circumcision Device for Male Population When Removing the Foreskin Shortly after Placement of Device*.; 2018.

39. Dalal S, Samuelson J, Reed J, Yakubu A, Baggaley R. Tetanus disease and deaths in men reveal need for vaccination. *Bull WHO*. 2016;94(March):613-621.

40. Scobie HM, Mao B, Buth S, et al. Tetanus immunity among women aged 15–39 years in Cambodia: A national population-based serosurvey, 2012. *Clin Vaccine Immunol*. 2016;(April):CVI.00052-16.

41. Dastur F, Awatramani V, Dixit S. Response to Single Dose of Tetanus Vaccine in Subjects with Naturally Acquired Tetanus Antitoxin. *Lancet*. 1981:219-222.

42. Bayas JM, Vilella A, Bertran MJ, et al. Immunogenicity and reactogenicity of the adult tetanus-diphtheria vaccine: How many doses are necessary? *Epidemiol Infect*. 2001;127(3):451-460.

43. Woldeamanuel YW, Andemeskel AT, Kyei K, Woldeamanuel MW, Woldeamanuel W. Case fatality of adult tetanus in Africa: Systematic review and meta-analysis. *J Neurol Sci*. 2016;368:292-299. doi:10.1016/j.jns.2016.07.025

44. Aziz R, Peck RN, Kalluvya S, Kenemo B, Chandika A, Downs JA. Tetanus in adult males, Bugando Medical Centre, United Republic of Tanzania. *Bull World Health Organ*. 2017;95(11):779-783.

45. Nanteza B, Galukande M, Aceng J, et al. The burden of tetanus in Uganda. *Springerplus*. 2016;5(1):705.

46. Zitelli J. Secondary intention healing : an alternative to surgical repair. *Clin dermatol*. 1984;2(3):92.

47. Barone MA, Ndede F, Li PS, et al. The Shang Ring Device for Adult Male Circumcision: A Proof of Concept Study in Kenya. *JAIDS J Acquir Immune Defic Syndr*. 2011;57(1):e7-e12.

48. Sokal DC, Li PS, Zulu R, et al. Field Study of Adult Male Circumcision Using the ShangRing in Routine Clinical Settings in Kenya and Zambia. *JAIDS J Acquir Immune Defic Syndr*. 2014;674:430-437.

49. Feldblum PJ, Zulu R, Linyama D, et al. Randomized Controlled Trial of the ShangRing for Adult Medical Male Circumcision : Safety , Effectiveness , and Acceptability of Using 7 Versus 14 Device Sizes. 2016;72:30-35.

50. Awori QD, Lee RK, Li PS, et al. Surgical outcomes of newly trained ShangRing circumcision providers. *J Acquir Immune Defic Syndr*. 2016;72:S13-S17.

51. Li P. ShangRing Circumcision App.
https://play.google.com/store/apps/details?id=com.wcg.wcm .

52. Mutabazi V, Kaplan S a, Rwamasirabo E, et al. One Arm, Open Label, Prospective, Cohort Field Study to Assess the Safety and Efficacy of the PrePex Device for Scale Up of Non-Surgical Circumcision when Performed by Nurses in Resource Limited Settings for HIV Prevention. *J Acquir Immune Defic Syndr*. 2013;63(3):315-322.

53. Bitega JP, Ngeruka ML, Hategekimana T, Asiimwe A, Binagwaho A. Safety and Efficacy of the PrePex Device for Rapid Scale up of Male Circumcision for HIV Prevention in Resource-Limited Settings. *J Acquir Immune Defic Syndr JAIDS*. 2011;58(5):e127-34.

54. UNAIDS. *Neonatal and Child Male Circumcision : A Global Review*.; 2010.

55. Builders P, Builders M. Wound care: Traditional Africal Medicine Approach. In: *Worldwide Wound Healing - Innovation in Natural and Conventional Methods Related*. Vol 2. Intech open; 2014:64.

56. Ojok F, Akise R. The impact of traditional treatments on wound care in sub-Saharan Africa. *Wounds Int*. 2012;3(1):7-8.

57. Grund J, Toledo C, Davis S, et al. Tetanus Cases After Voluntary Medical Male Circumcision for HIV Prevention — Eastern and Southern Africa, 2012–2015. *MMWR CDC Surveill Summ*. 2016;65(2):36-37.

58. Mavhu W, Hatzold K, Dam KH, et al. Adolescent Wound-Care Self-Efficacy and Practices after Voluntary Medical Male Circumcision - A Multicountry Assessment. *Clin Infect Dis*. 2018;66:S229-S235.

59. Price L, Liu C, Johnson K, et al. The Effects of Circumcision on the Penis Microbiome. *PLoS One*. 2010;5(1):e8422.

60. Liu CM, Hungate BA, Tobian AAR, et al. Male circumcision significantly reduces prevalence and load of genital anaerobic bacteria. *MBio*. 2013;4(2):1-9.

61. Liu CM, Prodger JL, Tobian AAR, Abraham AG, Price LB. crossm Penile Anaerobic Dysbiosis as a Risk Factor for HIV Infection. *MBio*. 2017;8(4):e00996-17.

62. Liu CM, Prodger JL, Tobian AAR, et al. Genital anaerobic bacterial overgrowth and the prepex male circumcision device, rakai, Uganda. *J Infect Dis*. 2016;214(4):595-598.

63. Musiige AM, Ashengo TA, Stolarsky G, et al. Participant experiences and views of odor and PrePex device removal pain in a VMMC pilot study in Botswana. *J Acquir Immune Defic Syndr*. 2016;72:S73-S77.

64. Mutabazi V, Bitega JP, Ngeruka LM, Karema C, Binagwaho A. Assessing odor level when using PrePex for HIV prevention: A prospective, randomized, open label, blinded assessor trial to improve uptake of male circumcision. *PLoS One*. 2015;10(5):1-10.

65. Kyu HH, Mumford JE, Stanaway JD, et al. Mortality from tetanus between 1990 and 2015 : findings from the global burden of disease study 2015. 2017:1-17.

66. Barone MA, Li PS, Awori QD, Lee R, Goldstein M. Clinical trials using the Shang Ring device for male circumcision in Africa: a review. *Transl Androl Urol*. 2014;3(1):113-124.

67. Cao D, Liu L, Hu Y, et al. A Systematic Review and Meta-analysis of Circumcision with Shang Ring vs Conventional Circumcision. *Urology*. 2015;85(4):799-804.

68. Bitega JP, Ngeruka ML, Hategekimana T, Asiimwe A, Binagwaho A. Safety and Efficacy of the PrePex Device for Rapid Scale up of Male Circumcision for HIV Prevention in Resource-Limited Settings. *J Acquir Immune Defic Syndr JAIDS*. 2011;58(5):e127-34.

69. Bochner AF, Feldacker C, Makunike B, et al. Adverse event profile of a mature voluntary medical male circumcision programme performing PrePex and surgical procedures in Zimbabwe. *J Int AIDS Soc*. 2017;20(1):1-6.

70. Galukande M, Nakaggwa F, Busisa E, Sekavuga Bbaale D, Nagaddya T, Coutinho A. Long term post PrePex male circumcision outcomes in an urban population in Uganda: A cohort study NCT02245126 NCT. *BMC Res Notes*. 2017;10(1):4-8.

71. Lebina L, Milovanovic M, Otwombe K, et al. PrePex circumcision surveillance: Adverse events and analgesia for device removal. *PLoS One*. 2018;13(3):1-10.

72. Feldacker C, Bochner AF, Murenje V, et al. Timing of adverse events among voluntary medical male circumcision clients: Implications from routine service delivery in Zimbabwe. *PLoS One*. 2018;13(9):e0203292.

73. Lebina L, Taruberekera N, Milovanovic M, et al. Piloting PrePex for adult and adolescent male circumcision in South Africa - Pain is an issue. *PLoS One*. 2015;10(9).

74. Milovanovic M, Taruberekera N, Martinson N, Lebina L. Perceptions of the PrePex device among men who received or refused prepex circumcision and people accompanying them. *J Acquir Immune Defic Syndr*. 2016;72:S78-S82. doi:10.1097/QAI.0000000000000703

75. Cummings B, Necochea E, Ferreira T, et al. Acceptability and satisfaction associated with the introduction of the prepex circumcision device in Maputo, Mozambique. *J Acquir Immune Defic Syndr*. 2016;72:S56-S62.

76. Feldblum PJ, Odoyo-June E, Bailey RC, et al. Factors associated with delayed healing in a study of the prepex device for adult male circumcision in Kenya. *J Acquir Immune Defic Syndr*. 2016;72:S24-S29.

77. Tshimanga M, Mangwiro T, Mugurungi O, et al. A phase II randomized controlled trial comparing safety, procedure time, and cost of the PrePex™ device to forceps guided surgical circumcision in Zimbabwe. *PLoS One*. 2016;11(5):1-15.

78. Odoyo-June, Elijah, Feldblum PJ, Fischer S, et al. Unexpected Complications Following Adult Medical Male Circumcision Using the PrePex Device. *Urologica*. 2016;96188-193.

79. Ndagijimana A, Mugenzi P, Thomson DR, Hedt-Gauthier B, Condo JU, Ngoga E. PrePex Male Circumcision: Follow-up and outcomes during the first two years of implementation at the Rwanda Military Hospital. *PLoS One*. 2015;10(9):1-9.

80. Feldblum PJ, Odoyo-June E, Obiero W, et al. Safety, effectiveness and acceptability of the PrePex device for adult male circumcision in Kenya. *PLoS One*. 2014;9(5).

81. Kerrin JC. The Distribution Of B . Tetani In The Intestines Of Animals. 1929;(1928):370-373.

82. Brook I. Genital Anaerobic Bacterial Overgrowth and the PrePex Male Circumcision Device, Rakai, Uganda. *J Infect Dis*. 2016;214(7):1125-1126.

83. Adamson PC, Tafuma TA, Davis SM, Xaba S, Herman-Roloff A. A systems-based assessment of the PrePex device adverse events active surveillance system in Zimbabwe. *PLoS One*. 2017;12(12):1-12.

84. Scobie HM, Patel M, Martin D, et al. Tetanus immunity gaps in children 5-14 years and men . ≥15 years of age revealed by integrated disease serosurveillance in Kenya, Tanzania, and Mozambique. *Am J Trop Med Hyg*. 2017;96(2):415-420.

85. Prodger JL, Kaul R. The biology of how circumcision reduces HIV susceptibility: Broader implications for the prevention field. *AIDS Res Ther*. 2017;14(1):1-5.

Appendix1: Results of Evidence Search

	Available data	Type of data	Evidence	Limitations/ strengths
1.	WHO TAG meeting/ teleconference reports 2015, 2016, 2017 [7–9]	Meeting reports	Tetanus incidence data from programme	Most likely complete source of data on tetanus incidence occurring in VMMC programme
2.	Tetanus in adult males, Bugando Medical Centre, United Republic of Tanzania [44]	Published literature	Incidence data regarding VMMC	One country only
3.	Tetanus disease and deaths in men reveal need for vaccination[39]	Published literature	Incidence data regarding VMMC	
4.	The burden of tetanus in Uganda[45]	Published literature	Background incidence of tetanus in one of the study populations	
5.	Mortality from tetanus between 1990 and 2015: findings from the global burden of disease study 2015[65]	Published literature	Background incidence of tetanus in one of the study populations	Only concerning deaths, data likely to be inaccurate
6.	WHO incidence data[8]	WHO reports	Tetanus incidence	Likely to be inaccurate
7.	Foreskin Shortly after Placement of PrePex Device performed at Lusaka and Livingstone, Zambia. Study Report January 24th, 2018[24]	Confidential report	PrePex Day 0 FRP procdure: Incidence data Wound healing data AE data Acceptability data	Follow-up for AEs only 7 days
8.	A safety and acceptability study of PrePex™ circumcision device among adolescent boys and adult men when foreskin is removed shortly after device placement [Day0 Foreskin Removal Procedure; Day0 FRP] (Intermediate Study Safety Report) January 31, 2018[25]	Confidential report		
9.	A Prospective, Randomized, Open Label Trial Comparing PrePex™ Day7 Foreskin Removal Procedure (FRP) to a PrePex Day0 FRP of Male Circumcision in Resource Limited Settings September 25th, 2017[26]	Confidential report		
10.	The Shang Ring Device for Adult Male Circumcision: A Proof of Concept Study in Kenya[47]	Published literature	Shang Ring procdure: Incidence data Wound healing data AE data Acceptability data	
11.	The acceptability and safety of the Shang Ring for adult male circumcision in Rakai, Uganda[35]	Published literature		
12.	Randomized trial of the Shang Ring for adult male circumcision with removal at one to three weeks: Delayed removal leads to detachment[33]	Published literature		
13.	Randomized Controlled Trial of the Shang Ring Versus Conventional Surgical Techniques for Adult Male Circumcision[34]	Published literature		
14.	Unpublished field study Kenya and Zambia HIV negative men 2013 [66]	Summarized in review article only		Full details not available
15.	Shang ring versus forceps-guided adult male circumcision: A randomized, controlled effectiveness study in Southwestern Uganda[36]	Published literature		

	Available data	Type of data	Evidence	Limitations/ strengths
16.	Randomized Controlled Trial of the ShangRing for Adult Medical Male Circumcision : Safety , Effectiveness , and Acceptability of Using 7 Versus 14 Device Sizes[49]	Published literature		
17.	Prospective Observational Study of the ShangRing Device for Adult Medical Male Circumcision in a Routine Clinical Setting in Malawi[37]	Published literature		
18.	A Systematic Review and Meta-analysis of Circumcision with Shang Ring vs Conventional Circumcision[67]			Data from studies above and mainly Chinese data (only 2 RCTs from Africa)
19.	The Safety and Acceptance of the PrePex Device for Non-Surgical Adult Male Circumcision in Rakai, Uganda. A Non-Randomized Observational Study[31]	Published literature	PrePex Day 7 procedure data	
20.	Safety and efficacy of the PrePex device for rapid scale-up of male circumcision for HIV prevention in resource-limited settings[68].	Published literature		
21.	Adverse event profile of a mature voluntary medical male circumcision programme performing PrePex and surgical procedures in Zimbabwe[69]	Published literature		
22.	Long term post PrePex male circumcision outcomes in an urban population in Uganda: a cohort study[70]	Published literature		
23.	PrePex circumcision surveillance: Adverse events and analgesia for device removal[71]	Published literature		
24.	Timing of adverse events among voluntary medical male circumcision clients: Implications from routine service delivery in Zimbabwe[72]	Published literature		
25.	Piloting PrePex for Adult and Adolescent Male Circumcision in South Africa –Pain Is an Issue[73]	Published literature		
26.	Perceptions of the PrePex Device Among Men Who Received or Refused PrePex Circumcision and People Accompanying Them[74]	Published literature		
27.	Participant Experiences and Views of Odor and PrePex Device Removal Pain in a VMMC Pilot Study in Botswana.[63]	Published literature		
28.	Acceptability and satisfaction associated with the introduction of the prepex circumcision device in Maputo, Mozambique[75]	Published literature		
29.	Safety, Feasibility, and Acceptability of the PrePex Device for Adult Male Circumcision in Malawi.[30]	Published literature		
30.	Safety and Efficacy of the PrePex Male Circumcision Device: Results From Pilot Implementation Studies in Mozambique, South Africa, and Zambia[28]	Published literature		
31.	Safety Profile of PrePex Male Circumcision Device and Client Satisfaction With Adolescent Males Aged 13-17 Years in Zimbabwe[29]	Published literature		
32.	Factors Associated With Delayed Healing in a Study of the PrePex Device for Adult Male Circumcision in Kenya[76]	Published literature	Wound healing	
33.	A Phase II Randomized Controlled Trial Comparing Safety, Procedure Time, and Cost of the PrePex™	Published literature	AEs	

	Available data	Type of data	Evidence	Limitations/ strengths
	Device to Forceps Guided Surgical Circumcision in Zimbabwe[77]			
34.	Unexpected Complications Following Adult Medical Male Circumcision Using the PrePex Device[78]	Published literature	Wound healing AEs	
35.	PrePex Male Circumcision: Follow-Up and Outcomes during the First Two Years of Implementation at the Rwanda Military Hospital[79]	Published literature		
36.	Safety, effectiveness and acceptability of the PrePex device for adult male circumcision in Kenya[80]	Published literature		
37.	One-arm, open-label, prospective, cohort field study to assess the safety and efficacy of the PrePex device for scale-up of nonsurgical circumcision when performed by nurses in resource-limited settings for HIV prevention[52]	Published literature		
38.	HIV Prevention: Male Circumcision Comparison Between a Nonsurgical Device to a Surgical Technique in Resource-Limited Settings: A Prospective, Randomized, Nonmasked Trial[27]	Published literature		
39.	The Distribution Of B. Tetani In The Intestines Of Animals [81]	Published literature	Microbiological environment	
40.	The Effects of Circumcision on the Penis Microbiome[59]	Published literature		
41.	Male circumcision significantly reduces prevalence and load of genital anaerobic bacteria[60]	Published literature		
42.	Penile Anaerobic Dysbiosis as a Risk Factor for HIV Infection[62]	Published literature		
43.	Genital Anaerobic Bacterial Overgrowth and the PrePex Male Circumcision Device, Rakai, Uganda[62]	Published literature		
44.	Genital Anaerobic Bacterial Overgrowth and the PrePex Male Circumcision Device, Rakai, Uganda[82]	Letter in Published literature		
45.	Assessing Odor Level when Using PrePex for HIV Prevention: A Prospective, Randomized, Open Label, Blinded Assessor Trial to Improve Uptake of Male Circumcision[64]	Published literature	Odor	
46.	WHO Technical Advisory Group on Innovations in Male Circumcision. Use of devices for adult male circumcision in public health HIV prevention programmes: conclusions of the Technical Advisory Group on Innovations in Male Circumcision. Geneva, Switzerland: WHO, 2012	WHO Paper	Standards for new devices and evaluation pathway	
47.	Safety and Acceptability of the PrePex Device When Used in Routine Male Circumcision Service Delivery During Active Surveillance in Zimbabwe[32]	Published literature	Feasibility of surveillance Incidence of AEs	
48.	A systems-based assessment of the PrePex device adverse events active surveillance system in Zimbabwe[83]	Published literature	Feasibility of surveillance	
49.	Tetanus immunity gaps in children 5-14 years and men ≥15 years of age revealed by integrated disease serosurveillance in Kenya, Tanzania, and Mozambique[84]	Published literature	Population immunity	

	Available data	Type of data	Evidence	Limitations/ strengths
50.	Notes from the Field: Tetanus Cases After Voluntary Medical Male Circumcision for HIV Prevention--Eastern and Southern Africa, 2012-2015. MMWR[57]	Published literature		
51.	The biology of how circumcision reduces HIV susceptibility: Broader implications for the prevention field[85]	Published literature		
52.	The impact of traditional treatments on wound care in sub-Saharan Africa[56]	Published literature		
53.	Wound care: Traditional African Medicine Approach[55]	Published literature		
54.	Adolescent Wound-Care Self-Efficacy and Practices after Voluntary Medical Male Circumcision - A Multicountry Assessment[58]	Published literature		
55.	Surgical outcomes of newly trained ShangRing circumcision providers[50]	Published literature		
56.	Field study of adult male circumcision using the ShangRing in routine clinical settings in Kenya and Zambia[48]	Published literature		
57.	ShangRing Circumcision App[51]	Training material		

Appendix 2: Tetanus case SAE

SAE report of possible mild tetanus case

Reviewing the reports concerning the suspected case of tetanus, there are several inconsistencies and errors.

1. Page 29 of the study report detailing the SAE states "Investigation of the SAE by the PrePex™ device manufacturer (Appendices 8.2.2 and 8.2.8) and Expert opinions (Appendix 8.2.6), concluded that the SAE is not associated with the MC procedure nor the PrePex device. This conclusion has been approved by WHO (Appendix 8.2.9)." Personal communication with WHO staff, establishes that WHO 'approval' was confined to due processes being implemented i.e. that an investigation into the root cause of the adverse event had been conducted according to documented SOP. WHO has not confirmed that the SAE is not associated with the MC procedure nor the PrePex device. (WHO statement: 'from our point of view, CMT has enacted their documented procedure for complaint investigation and the processes/procedures in place appear to have been implemented.')
2. The Participant Incident/Severe Adverse Event Report form submitted by the study clinician [Document page 55] states that "*upon review the physician made a diagnosis of mild tetanus…There was no episode of spasms*". Consultant Physician Aga Khan Hospital Kistumu's medical report of 20/10/17 however states that on admission *"the main findings were spasms of the muscles of the back of the chest*."
3. The form states "*Drugs prescribed at the time of admission were …IM valium*" [Page 55] Consultant Physicians's report 20/10/17 stated the patient was given intravenous diazepam.
4. The form also notes *"Tetanus swab for culture and sensitivity. The swab was not taken due to lack of secretion on the circumcision wound*" [Page 56]. The Consultant Physician's medical report 6/11/17 states that a "*fresh wet circumcision wound*" was present and that "*a swab from the wound did not grow any organisms*". In the report of 20/10/17 it also states that "*no growth was obtained*" from a swab taken.
5. The AE Manufacturer investigation reporting form notes that *"During admission there were no classic symptoms of tetanus such as muscle rigidty, spasms or locked jaw" [Page 60]*. The Consultant Physician's medical report of 20/10/17 states that on admission the patient complained of " *inability to fully open his mouth*" and that on examination *"the main findings were spasms of the muscles of the back of the chest*." In addition "*Mild risus sardonicus associated with inability to open his mouth wide*" was also noted. Therefore symptoms and signs of trismus are recorded in addition to clinical signs of muscle spasm and risus sardonicus (a characteristic feature of tetanus).
6. The form also notes that "*It appears that the patient experienced back and low neck pain in less than 24 hours after the device application procedure. The patient did not report this to the physician at the hospital on October 14th but only during interview on November 6th*" [Page 60]. It is notable that at this interview members present were study team and CMT representatives. At no other point – during earlier interviews or at the time of hospital admission was this noted and the records clearly document a 5-day history only.
7. In expert opinions provided by CMT, one professional consulted states "*At no time during admission ware any muscle spasm, rigidity and lockjaw noted*". Muscle spasm and lock jaw

were noted by the admitting doctor. Trismus and muscle spasm were clearly noted on admission to hospital as noted above.

8. The same professional states "*It [tetanus] is characterized by painful spasms, usually starting at the jaw and spreading to the neck back and abdominal wall. The spasms are usually initiated by stimuli light, touch, auditory or emotional stimuli. The participant did not have these symptoms"* Spasms of jaw, neck and back were reported. These were described as 'on-off' in the report of 20/10/17 which may suggest initiation by external stimuli.

9. It is stated on page 72 in expert opinion that "*Furthermore the classification of "MILD" tetanus using ABLETT classification of tetanus requires the presence of mild to moderate trismus in which the patient would not have been able to open his mouth; and generalized spasticity. The patient had none of these*" The Ablett classification for tetanus is a simple 4 point score often used in clinical studies. The score has never been validated regarding prognosis. Furthermore at no point have any of the medical reports declared they were using an ABLETT classification method to describe the severity of tetanus. As mentioned previously on interview at the clinic on 14th October the patient described "*mild difficulty opening his mouth when eating*". On admission to hospital the patient was noted in report of 20/10/17 and to complain of "*inability to fully open his mouth"* and on examination "inability to open his mouth wide" was noted indicating the presence of trismus.

10. Also on page 72 is the statement "*The patients' response to treatment was dramatic, occuring in 4 days from the start of the clinical condition. In tetanus, with treatment, spasms typically reduce after 2-3 weeks but stiffness may persist considerably longer*" In severe tetanus spasms typically last 2-3 weeks, but in mild tetanus (Ablett Grade 1 or 2) there are no spasms or mild spasms which are usually abolished by diazepam. The patient was discharged home still on oral diazepam (10mg daily). There is no note about whether this is for ongoing rigidity. Case reports exist in the literature of tetanus-associated trismus improving within 3 days.[1]

11. The expert consulted states that the "presentation and response to treatment does not match what would be tetanus" The patient had trismus, dysphagia, risus sardonicus and muscle spasms. These are all classic and characteristic features of tetanus. What makes the case difficult is that the spasms were confined to the chest, neck and masseter muscles.

12. A second expert opinion provided by CMT states " *The spasm characteristic of generalized tetanus are initiated by external stimuli such as light/noise and the study participant did not have any of these symptoms*." Whist this may be true, often in tetanus spasms are not obviously initiated by external stimuli. The patient was noted nevertheless in the Consultant Physician's report of 20/10/17 to have "*muscle spasms over the back of the chest that come on and off*"

13. This second expert states that "*the white cell count was not indicative of infection since this was not raised*". A raised white cell count does not usually occur in tetanus. Data from an observational study showed that in 2393 patients with tetanus median and interquartile range of white blood cell count at hospital admission were normal [2].

14. The second expert also states that the incubation period was "*too long for tetanus the average incubation period is 7-10 days). The patient presented at 22 days post circumcision*". This does not exclude the possibility that infection occurred after the initial procedure. Indeed if the procedure was carried out to the correct standard, infection should not occur at this point.

15. Finally the second expert states "*The blood pressure has always been documented as normotensive whilst the pulse rate remained relatively constant. These are atypical presentations since tetanus presents with autonomic instability*". Autonomic instability classically occurs later in the course of tetanus (towards the end of the 1st week or 2nd week of disease). Mild tetanus is not associated with clinically apparent autonomic instability [3]. In a prospective randomized controlled trial of patients with tetanus only 1/97 had clinically apparent autonomic instability on admission [4]. In a prospective study of 197 patients with severe tetanus (Ablett Grade 3 and 4) mean systolic was BP 120 mmHg indicating normotension is common even in severe tetanus [5].

16. A third expert opinion provided by CMT states that "*there were no spastic contractions*". Spasms were however noted by the Consultant Physicians in the report of 20/10/17. However, in mild tetanus no spasms are present. In Patel's study of 8,697 patients with tetanus, 2100 did not develop muscle spasms [6]. It is argued that prompt treatment with benzodiazepines will ameliorate frank spasms.

17. The expert states "*there was no obvious portal of entry of C. tetani through skin wound or circumcision site*". There was a circumcision wound noted (and visible in photographs). Regarding likely entry sites of tetanus, preliminary results from a prospective observational study of 100 adult patients with tetanus admitted to the Hospital for Tropical Diseases with tetanus in 2017, has shown that of 55 patients where an entry site was identified by treating physicians and a wound swab was taken, 26 (47%) cultured positive for *C. tetani,* and the remainder were negative. Thus a negative swab does not exclude the diagnosis of tetanus (personal communication Mr James Campbell, microbiologist, Oxford University Clinical Research Unit).

    In addition to the wound noted by the Consultant Physicians from which a swab was taken, no other wounds were seen. It is also notable that at the day 14 visit to the clinic, the report states that "*the alarming concern on this day was mild smell from the circumcision site*".

18. The expert gives the opinion that "*because the patients' symptoms were in the upper part of the body it is unlikely due to C. tetani infection of the circumcision site*". Irrespective of wound site, proximal muscles are typically affected first in tetanus – possibly due to the shorter neuronal pathways. Therefore the absence of distal symptoms and signs does not exclude tetanus [7].

Expert Opinion

For a second opinion on likelihood of tetanus diagnosis and possible entry site, case records were examined by an experienced infectious disease/ critical care physician with > 25 years' experience working in a tetanus unit with 200-300 admissions/year and author of > 20 publications on tetanus.

"The relevant history is

1. Device placed on 22nd September
2. 28th September device removed
3. 6th October mild smell noted: no pain and no fever
4. 9th October developed trismus

5. On admission to hospital there was a history of trismus neck and back pain and rigidity, difficulty swallowing and risus sardonicus. Circumcision wound present
6. Treated with intravenous and oral diazepam and symptoms improved. Also remained conscious on this medication.

In my opinion we cannot exclude the diagnosis of mild tetanus. A doctor experienced in tetanus also diagnosed this. I do not think it due to the device placement itself but the entry site is the circumcision wound. Wound hygiene may have contributed."

Root Cause Analysis Report (Section 8.2.8)

The conclusions of this report are not a fair reflection of expert opinion in this case.

1. *"It is very likely[1] that the root* cause for the symptoms of the participant (right sided chest pain, neck pain) was due t*o respiratory infection or previous injury during work (tire explosion) and not due to tetanus / mild tetanus*. [1] "Very likely" means greater than 90 percent."
   This is not the opinion of most experts consulted or the two physicians who saw and examined the patient:
   The consultant physician and study physician: the two physicians who examined the patient diagnosed mild tetanus.
   One expert consulted concluded there "was no evidence to conclude with certainty this patient had mild tetanus. It is possible it may have been myalgia caused by a viral infection or upper respiratory tract bacterial infection."
   A second expert concludes "The diagnosis of tetanus has been made in the absence of more advanced testing. There is no evidence to conclude with certainty this patient had mild tetanus".
   A third expert concludes "Although mild tetanus is a likely diagnosis….The patients symptoms could also be due to viral or upper respiratory bacterial infection".

   Regarding the diagnosis of upper respiratory infection, the patient had no fever or upper respiratory tract infection symptoms (notably no symptoms of cough or runny nose or sore throat).

2. "*It is extremely likely[2] that, even if the participant had mild tetanus, neither the Prepex device nor the circumcision procedure were the root cause of this event, namely, they were not the port of entry of the C. tetani*. [2] "Extremely likely" means greater than 95 percent."

   Whilst most experts are in agreement that it is unlikely that infection occurred at the time of placement. The consultant physician, study physician, third expert and independent expert have noted that the circumcision wound is a possible or probably entry site. In addition

   1. A wet oozing circumcision wound was noted on admission
   2. No other wound was present
   3. Prior to symptom onset odour was noted coming from the wound

WHO have published clear criteria to determine consistency of cases with causality[8]. Criteria which are 'consistent with causality' are as follows:

1. Signs and symptoms of tetanus after circumcision that occur within a plausible incubation period for *C. tetani* (at least one and no more than 112 days)
   AND
   I. Circumcision wound site infection
   II. History applying substance potentially containing tetanus spores to wound
   III. A reportedly normal healing wound an no alternative tetanus entry points (for example puncture or wounds conducive to tetanus) evident elsewhere on body

OR surgical equipment demonstrated to contain *C. tetani* spores

Given expert opinion state that tetanus cannot be excluded, symptoms occurred within 112 days and there is a reportedly normal healing wound with no alternative tetanus entry points seen, this case meets these criteria.

References

1. Shota Yamasaki S, Tsukita K, Wada I,Suenaga T. Tetanus-induced Trismus: Improvement on a Daily Basis. Intern Med. 2017 Oct 15; 56(20): 2813–2814.
2. Thwaites CL, Yen LM, Glover C, et al. Predicting the clinical outcome of tetanus: the tetanus severity score. *Trop Med Int Heal*. 2006;11(3):279-287.
3. Thwaites CL, Yen LM, Cordon SM, et al. Urinary catecholamine excretion in tetanus. *Anaesthesia*. 2006;61(4):355-359.
4. Miranda-Filho DDB, Ximenes RADA, Barone AA, Vaz VL, Vieira AG, Albuquerque VMG. Randomised controlled trial of tetanus treatment with antitetanus immunoglobulin by the intrathecal or intramuscular route. *BMJ*. 2004;328(7440):615.
5. Thwaites CL, Yen LM, Loan HT, et al. Magnesium sulphate for treatment of severe tetanus: a randomised controlled trial. *Lancet*. 2006;368(9545):1436-1443
6. Patel JC, Mehta BC. Tetanus: study of 8,697 cases. *Indian J Med Sci*. 1999;53:393-401.
7. Udwadia FE. *Tetanus*. Oxford University Press; 1994.
8. World Health Organization (WHO). WHO Informal Consultation on Tetanus and Voluntary Medical Male Circumcision: Report of Meeting Convened in Geneva, Switzerland, 9-10 March 2015.; 2015.